1. SYNOPSIS/ABSTRACT

TITLE

FINAL REPORT - OBSERVATIONAL SAFETY AND EFFECTIVENESS STUDY OF PATIENTS WITH POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH TOCILIZUMAB

KEYWORDS

Polyarticular juvenile idiopathic arthritis, Tocilizumab, Adverse Events of Special Interest, Feeder Registries.

RATIONALE AND BACKGROUND

As per the EU post-authorization measure (PAM) Category 3 study in the EU Risk Management Plan and the US post marketing requirement (PMR) 2678-2, a long-term safety study (WA29358) was initiated to address the Health Authorities' concerns regarding long-term safety risks in pediatric patients (aged 2-17 years) with polyarticular juvenile idiopathic arthritis (pJIA) treated with tocilizumab (TCZ). The study included a control group of pediatric pJIA patients treated with other biologics as standard of care. Patients were followed for 5 years.

This Final Report presents a summary of aggregate data received from three feeder registries (Childhood Arthritis and Rheumatology Research Alliance [CARRA], Juvenile arthritis Methotrexate/ Biologics long-term Observation [JuMBO], and Biologics in Pediatric Rheumatology Registry [BiKeR]) up to five years.

OBJECTIVE

The overall objective of the study was to assess the long-term safety and effectiveness of TCZ (IV or SC) in relation to a comparator biologic in the treatment of pJIA in a real-world setting for 5 years.

AMENDMENT AND UPDATES TO PROTOCOL

There have been 6 amendments made to the protocol for Study WA29358.

STUDY DESIGN

The study allowed for analysis of aggregate data from approximately 600 patients (approximately 300 patients each treated with TCZ and a comparator biologic) with pJIA (defined as RF-positive pJIA, RF-negative pJIA, or oligoarticular juvenile idiopathic arthritis [eoJIA] per International League of Associations of Rheumatology [ILAR]) classification, who were enrolled in national disease or treatment registries (i.e., feeder registries [CARRA, JuMBO and BiKeR]) in the United States and Germany, at approximately 100 sites.

The observation period for this study was defined as a maximum of 5 years and data for the study was collected directly from the feeder registries. Patients who switched therapy or discontinued therapy during the observation period were continued to be followed in accordance with the feeder registry protocols to allow for long-term safety assessment up to the maximum period of 5 years.

The study start was the start of data collection by the feeder registries and the study end was the receipt of the 5-year aggregate data from the registries by the Sponsor.

SETTING

This was an international, multicenter, prospective, observational-cohort study, designed to examine long-term safety and effectiveness data in a real-world setting. Data was obtained from patients enrolled in active national disease or treatment registries (feeder registries) located in the United States and the Germany.

SUBJECT AND STUDY SIZE (INCLUDING DROPOUTS)

Aggregate data was collected from a sample size of 344 patients with pJIA receiving TCZ (IV or SC), and another 345 patients with pJIA receiving a comparator biologic.

DATA SOURCES

Patient data was collected by the feeder registries via paper or electronic Case Report Forms. The feeder registries were responsible for management of the data they collected, including the quality check of the individual data points. While patient level data was not transferred to the Sponsor, the feeder registries shared aggregate data reports at annual intervals and at the 5-year timepoint with the Sponsor.

RESULTS

A total of 344 patients and 345 patients were enrolled in the TCZ cohort and Non-TCZ cohort of the study, respectively.

The total number of patients who discontinued from the study was comparable between the TCZ and Non-TCZ cohorts. The main reason for treatment discontinuation from the TCZ cohort was ineffectiveness (lack of primary response) and from the Non-TCZ cohort was disease well-controlled.

The baseline demographic characteristics were comparable between the TCZ and Non-TCZ cohorts. Mean age at baseline for the patients enrolled in the TCZ cohort was 12.40 years and in the Non-TCZ cohort was 11.01 years.

The distribution of males and females was balanced across both study cohorts. In terms of race, the majority of participants in both cohorts were White. The distribution of patient weight at baseline showed that the TCZ cohort had a larger proportion of patients weighing ≥ 30 kg compared to the Non-TCZ cohort.

The TCZ cohort represented a highly treatment-refractory population; 86.3% of TCZ patients had prior biologic exposure at baseline, compared to only 23.5% in the Non-TCZ cohort. In both cohorts, the most prevalent baseline disease status was RF-negative followed by eoJIA and RF-positive status.

Uveitis, other major congenital or acquired disease/condition, upper respiratory tract infection and asthma were the major preferred terms reported in the medical history for both TCZ and Non-TCZ cohorts. Fibromyalgia was one of the most reported comorbid events in both the cohorts. Methotrexate was the most frequently used concomitant medication.

Adverse Events of Special Interest (AESI) reported during the study were serious infections, serious cardiovascular events and non-serious uveitis events. In two of the uveitis cases, treatment with TCZ was discontinued, and in four cases the dosing remained unchanged. There were no reports of AESIs for malignancies (serious or non-serious), serious gastrointestinal (GI) perforations or serious uveitis. The incidence rate of serious infections and cardiovascular events was comparable in both the TCZ and Non-TCZ cohorts.

The number of serious adverse events (SAEs) reported in the TCZ cohort was higher than in the Non-TCZ cohort.

Deaths reported during the study period in a patient exclusively in non-TCZ cohort ($n = 1$) as well as in a patient exposed to both the cohorts ($n = 1$) reported.

Interpretation and comparison of development patterns observed were not meaningful as patients in the TCZ cohort were older at treatment start as compared to the Non-TCZ cohort. The difference in height standard deviation scores (SDS) observed between the cohorts over the 5 years was comparable. Overall, mean height velocity was lower in the TCZ cohort as compared to the Non-TCZ cohort.

Most patients in Stages 1-4 at baseline had an increase in Tanner stage during follow-up in both the TCZ and Non-TCZ cohorts.

Progressive improvement in the Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10) score was observed throughout the study period from baseline to Year 5 in evaluable patients in the TCZ cohort.

DISCUSSION

The findings from Study WA29358, based on a cumulative analysis of combined aggregate data from the observational CARRA, JuMBO, and BiKeR feeder registries, provide robust real-world evidence supporting the long-term safety and effectiveness of tocilizumab (IV or SC) in relation to comparator biologics in pediatric patients with pJIA. Overall, the long-term safety data,

including the occurrence of protocol-specified AESIs, are in line with the known safety profile of TCZ. Real-world effectiveness of TCZ was demonstrated by a reduction in JADAS-10 scores.

The results of Study WA29358 support a positive safety and effectiveness profile for the long-term use of TCZ in pediatric patients with pJIA, reflective of routine clinical practice. The safety profile of TCZ as observed in this study is aligned with the current labeling for TCZ in the United States Prescribing Information (USPI) and Summary of Product Characteristics (SmPC).

CONCLUSION

This 5-year real-world study confirms a favorable long-term benefit-risk profile for TCZ in pediatric patients with pJIA, aligning with current labeling.

Safety and AESIs: No increased risk of atherosclerosis, malignancies, or GI perforations was observed. Serious infection rates were very low and identical to the comparator group. TCZ demonstrated a lower incidence of uveitis despite a more refractory baseline population with no serious cases and observations failing to support a direct causal link.

Growth and Development: Continuous TCZ treatment does not adversely impact physical or pubertal development; rather, it facilitates the normalization of growth (height SDS) by Year 5 through effective inflammation control.

Efficacy: The 10 mg/kg IV Q4W (and SC) regimen provides durable disease control (JADAS-10), demonstrating effectiveness even in highly treatment-refractory patients who previously failed TNF-inhibitors, regardless of RF status.

The clinical benefits of TCZ observed in controlled trials translate effectively to real-world practice with no new safety signals identified over long-term exposure.